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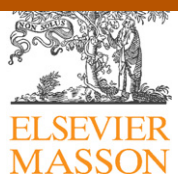

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CLINICAL RESEARCH

Aortic root dilatation in young patients with cryptogenic stroke and patent foramen ovale

Dimensions aortiques chez les patients avec foramen ovale perméable ayant présenté un accident vasculaire cérébral idiopathique

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KEYWORDS
Patent foramen ovale;
Cryptogenic stroke;
Aortic root dilatation

Summary
Background. — No previous study has looked for an association between aortic dilatation and the clinical sequelae of patent foramen ovale (PFO), although a possible relationship has been identified in case reports.
Aim. — To compare aortic dimensions in patients with symptomatic PFO and healthy controls.
Methods. — Forty-seven patients were identified who presented with cryptogenic cerebrovascular accident (CVA) assessed as most likely secondary to PFO (confirmed by contrast study), were aged less than 50 years and underwent percutaneous PFO closure. Forty-seven age-, sex- and body surface area-matched healthy controls were also identified.
Results. — Aortic root diameters were greater in PFO patients. The difference was more marked at the levels of the sinuses of Valsalva (34 ± 4 vs 31 ± 3 mm, $P < 0.01$) and the proximal ascending aorta (32 ± 4 vs 29 ± 3, $P < 0.01$) and more modest at the level of the aortic annulus (23 ± 3 vs 22 ± 2 mm, $P = 0.20$). In addition, patients with massive right-to-left shunting tended to have larger aortic diameters. In contrast, left ventricular end-systolic and end-diastolic diameters were not larger than in controls (30 ± 4 vs 32 ± 5 mm, $P = 0.10$ and 48 ± 5 vs 50 ± 4 mm, $P = 0.04$, respectively).

Abbreviations: ASA, atrial septal aneurysm; BSA, body surface area; CVA, cerebrovascular accident; IAS, interatrial septum; PFO, patent foramen ovale; TTE, transthoracic echocardiography.

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Conclusion. — The present study shows that aortic diameter is increased in young patients with cryptogenic CVA and PFO compared with in healthy subjects. Our results suggest that aortic dilatation may potentiate the risk of CVA in PFO patients and support further research in this area.

MOTS CLÉS
Foramen ovale perméable ;
Accident vasculaire cérébral ;
Dilatation de l'aorte

Résumé
Contexte. — Il n'existe pas d'étude ayant évalué la relation entre la taille de l'aorte ascendante et la présence d'un foramen ovale perméable (FOP) symptomatique, même si une telle association a été suggéré dans des cas cliniques.
Objectifs. — Le but de cette étude était de comparer les dimensions de l'aorte chez des patients avec un FOP ayant présenté un accident vasculaire cérébral (AVC) et chez des sujets sains.
Méthodes. — Nous avons inclus 47 patients ayant : 1 : présenté un AVC sans autre cause retrouvé qu'un FOP confirmé par épreuve de contraste ; 2 : agés de moins de 50 ans et ; 3 : ayant bénéficié d'une fermeture percutanée du FOP et 47 sujets sains comme contrôles appariés pour l'âge, le sexe et la surface corporelle.
Résultats. — Les diamètres aortiques etaient significativement plus large chez les patients avec FOP que chez les contrôles. Les différences étaient surtout marquées au niveau des sinus de Valsalva (34 ± 4 vs 31 ± 3 mm, $p < 0{,}01$) et de l'aorte tubulaire (32 ± 4 vs 29 ± 3, $p < 0{,}01$) et moins au niveau de l'anneau (23 ± 3 vs 22 ± 2 mm, $p = 0{,}20$). Les patients avec un shunt important présentaient également des dimensions aortique plus importantes. À l'inverse, les dimensions ventriculaires n'étaient pas plus large chez les patients que chez les contrôles (30 ± 4 vs 32 ± 5, $p = 0{,}10$ et 48 ± 5 vs 50 ± 4 mm, $p = 0{,}04$, respectivement).
Conclusions. — Cette étude montre que les dimensions aortiques sont plus importantes chez les patients avec FOP ayant présenté un AVC idiopathique que chez les sujets contrôles. Ces résultats suggèrent que la dilatation aortique pourrait être un facteur favorisant d'AVC chez les patients présentant un FOP et nécessite des études complémentaires.

Introduction

Patent foramen ovale (PFO) has been linked with an increased risk of cerebrovascular accident (CVA) in case-controlled studies [1,2], especially when associated with an atrial septal aneurysm (ASA) [3,4]. However, PFO is a common finding in the general population (up to 25%) [5,6] and factors that may potentiate the risk of stroke (in addition to the presence of a PFO) are of great interest [7—9]. Case reports [10—13] and one retrospective series [14] have indicated a possible association between aortic root dilatation (particularly aneurysm formation) and right-to-left shunting. However, no previous study has looked for an association between aortic dilatation and the clinical sequelae of PFO. Thus, the aim of the present study was to compare aortic dimensions in patients with symptomatic PFO and in healthy controls hypothesizing that they would be larger in patients with PFO.

Methods

Population

Patients who have undergone PFO closure at our institution are enrolled into a database, which was reviewed to identify patients who presented with cryptogenic CVA as defined by the referring neurologist, had a PFO confirmed by a transthoracic echocardiography (TTE) contrast study, were aged less than 50 years and underwent percutaneous PFO closure. The database was reviewed for clinical variables including height, weight, body surface area (BSA), modifiable cardiovascular risk factors, history of migraine and the presence of ASA. Patients with PFO were matched for age, sex and BSA with healthy volunteers (nurses, medical students, physicians) with no previous medical history, who were not taking any medication and had no modifiable cardiovascular risk factors.

Echocardiographic analysis

TTE was performed using high-quality commercially available ultrasound systems (iE33 [Royal Philips Electronics, Amsterdam, The Netherlands] and Vivid 7 [GE Healthcare, Chalfont St. Giles, UK]). A PFO was considered present when a contrast test with agitated saline solution, at rest and during a Valsalva manoeuvre, showed an interatrial shunt with an early (within three cardiac cycles) opacification of the left atrium [3]. ASA was defined as an interatrial septum (IAS) of abnormal mobility with protrusion of the septum into the left or right atrium by at least 10 mm beyond the baseline [15]. Measurements of the aortic root and proximal ascending aorta were made retrospectively using the same methodology in controls and patients, from two-dimensional digitalized images and videos stored on the network, in the parasternal long-axis view, perpendicular to the long axis of the vessel, from leading edge to leading edge by one operator. Measurements were made at three levels: the aortic

annulus, the sinuses of Valsalva and the proximal ascending aorta, 1 cm above the sinotubular junction. As is conventional, the aortic annulus diameter was measured at end systole, while the diameters at the sinuses of Valsalva and in the proximal ascending aorta were measured at end diastole [16,17]. In addition, left ventricular end-diastolic and end-systolic diameters were measured in the parasternal long-axis view using M-mode.

Statistics and ethics

Continuous variables are expressed as mean ± standard deviation. Comparisons between PFO patients and controls were performed using the *t* test or the Khi^2 test, as appropriate. Variability in diameter measurements was calculated at each level (aortic annulus, sinuses of Valsalva and proximal ascending aorta) as the absolute difference between measurements performed weeks apart by the same operator (intraobserver variability) or different operators (interobserver variability). As this was a retrospective analytical study and the patients required no additional investigations, only verbal consent was obtained. Healthy controls are enrolled in an ongoing prospective study.

Results

Baseline characteristics

Between September 2006 and July 2009, 47 PFO patients with cryptogenic CVA and PFO met the enrolment criteria and were matched with 47 healthy controls. The characteristics of both populations are given in Table 1. By design, there were no significant differences between populations in terms of age, sex, height, weight or BSA. No PFO patient was hypertensive. Nine (19%) PFO patients had a history of migraine, 35 (74%) met the diagnostic criteria for ASA and 23 (49%) had massive right-to-left shunting, as indicated by the passage of greater than 30 microbubbles spontaneously without a Valsalva manoeuvre during a TTE contrast study.

Echocardiographic measurements

Aortic root diameters were greater in patients with PFO. The difference was more marked at the levels of the sinuses of Valsalva (34 ± 4 vs 31 ± 3 mm, $P < 0.01$) and the proximal ascending aorta (32 ± 4 vs 29 ± 3 mm, $P < 0.01$); the difference was non-significant at the level of the aortic annulus (23 ± 3 vs 22 ± 2 mm, $P = 0.20$) (Fig. 1) (Table 1). In contrast, left ventricular diameters were not greater in PFO patients. There was no significant difference in left ventricular end-systolic diameters between PFO and control patients (30 ± 4 vs 32 ± 5 mm, $P = 0.10$), whereas left ventricular end-diastolic diameters were slightly greater in healthy controls (48 ± 5 vs 50 ± 4 mm, $P = 0.04$). Aortic diameters were larger in patients with massive right-to-left shunting than in those with more modest shunting at the level of the proximal ascending aorta (33 ± 4 vs 30 ± 4 mm, $P = 0.05$) but not at the levels of the aortic annulus (23 ± 2 vs 23 ± 3 mm, $P = 0.87$) and the sinuses of Valsalva (33 ± 4 vs 34 ± 5 mm, $P = 0.48$). There was also a trend toward larger proximal ascending aorta diameters in patients with ASA compared with in patients with isolated PFO (34 ± vs 31 ± 4 mm, $P = 0.11$).

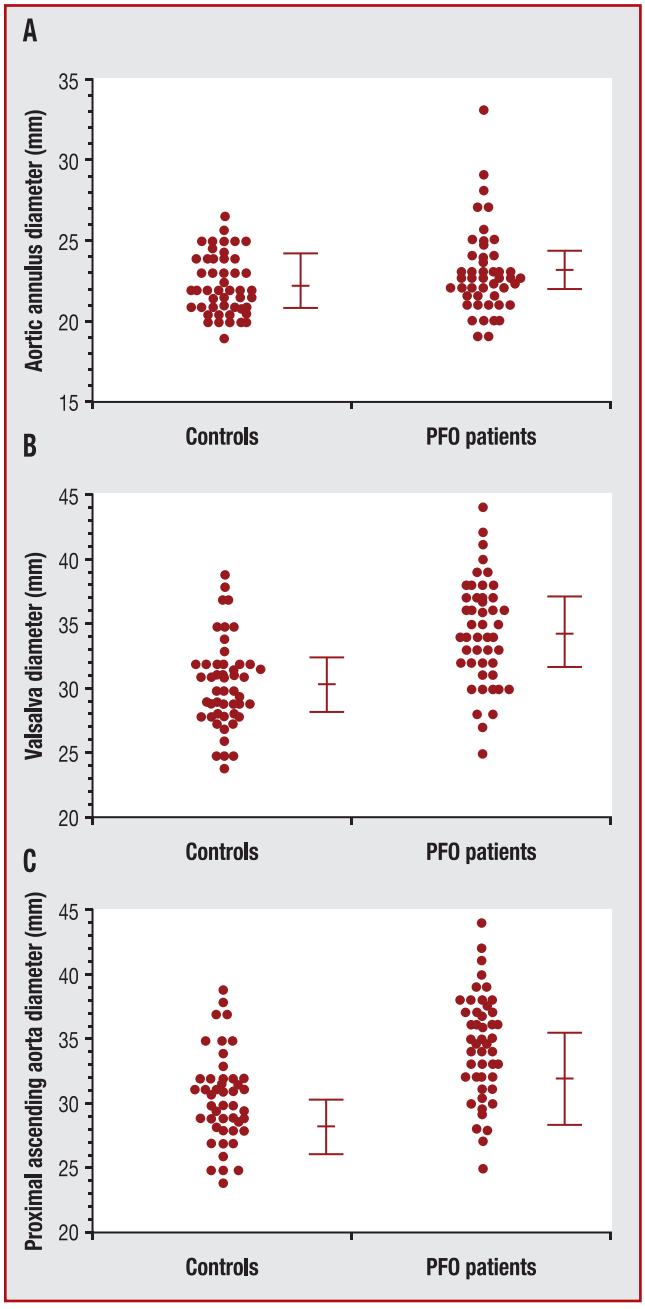

Figure 1. Scatterplots of diameters of (A) the aortic annulus, (B) the sinuses of Valsalva and (C) the proximal ascending aorta, in controls and patients with patent foramen ovale (PFO). Bars represent the 25th, 50th and 75th percentile values.

Intra- and interobserver variability

Intra- and interobserver variabilities at the levels of the aortic annulus, the sinuses of Valsalva and the proximal ascending aorta were 0.7 ± 0.9 mm, 0.9 ± 1.1 mm and 0.7 ± 1.1 mm and 0.8 ± 0.8 mm, 1.5 ± 1.3 mm and 0.6 ± 0.9 mm, respectively.

Table 1 Clinical and echocardiographic characteristics of healthy subjects and patients with patent foramen ovale.

	Healthy volunteers ($n = 47$)	Patients with patent foramen ovale ($n = 47$)	*P*
Age (years)	35 ± 12	37 ± 7	0.3
Men	27 (57)	28 (60)	0.8
Height (m)	1.72 ± 0.09	1.72 ± 0.10	0.9
Weight (kg)	72 ± 11	74 ± 14	0.4
Body surface area (kg/m²)	1.85 ± 0.16	1.88 ± 0.21	0.5
End-diastolic left ventricular diameter	50 ± 4	48 ± 5	0.10
End-systolic left ventricular diameter	32 ± 5	30 ± 4	0.04
Aortic diameters			
Aortic annulus	22 ± 2	23 ± 3	0.2
Sinuses of Valsalva	31 ± 3	34 ± 4	< 0.01
Proximal ascending aorta	29 ± 3	32 ± 4	< 0.01

Values are mean ± standard deviation or number of patients (percentage).

Discussion

Aortic diameters at the levels of the sinuses of Valsalva and the aortic root were significantly greater in patients with cryptogenic CVA and PFO than in matched healthy controls. The size of the difference was about 10%. There was a trend towards an increased aortic annulus diameter that did not achieve statistical significance. These differences were specific to the aorta and PFO patients had similar left ventricular diameters.

PFO, an interatrial connection through the septum secundum that persists after birth, is common, with an incidence of about 25% of the population in both postmortem [5] and echocardiographic studies [6]. ASA refers to a hypermobile septum primum portion of the IAS, present in 2% of normal individuals and associated with right-to-left shunting in 83% [4]. However, despite its high prevalence and potential serious consequences, adjunctive factors that may predispose or potentiate the risk of CVA remain unclear.

In the present study, we observed larger aortic dimensions in patients with cryptogenic CVA and PFO than in healthy controls. Dilatation of the aortic root and proximal ascending aorta may increase the risk of right-to-left shunting by changing the angulation of the heart in such a way that flow streaming from the inferior vena cava into the right atrium is directed more towards the ostium secundum portion of the IAS; thrombotic material is therefore more likely to cross into the systemic circulation, possibly causing a CVA (Fig. 2). This is the explanation for the platypnoea-orthodeoxia syndrome and the association between aneurismal dilatation of the ascending aorta and massive right-to-left shunting in certain postures [10,13]. In a non-CVA population, the aortic root diameter has been found to be inversely correlated with the size of the IAS. As the IAS basal diameter gets smaller, it becomes more mobile and more prone to shunting [18]. In our opinion, these mechanistic factors are the most plausible explanation for our findings and it is worth noting that patients with massive right-to-left shunting tend to have larger aortic dimensions. In the present study, we did not measure IAS dimensions but they would be of interest to assess in a future prospective study of the relationship between IAS size, IAS mobility, degree of shunting and aortic dimensions in patients with cryptogenic CVA with and without PFO. A second potential explanation for our findings is that there is a common tissue disorder underlying PFO, ASA and aortic dilatation. Thus, ASA was observed almost three times more frequently in a cohort of Marfan patients than in healthy controls, which provides evidence that the presence of ASA may be related to a connective tissue disorder; however, the prevalence of PFO was not evaluated [19]. Finally, we cannot exclude a confounding factor among PFO patients with CVA that may explain aortic dilatation. We tried to exclude such confounding variables by excluding older PFO patients who might have vascular risk factors that could possibly explain both the CVA and aortic dilatation. In this regard, it should be emphasized that no PFO patient or healthy control was hypertensive.

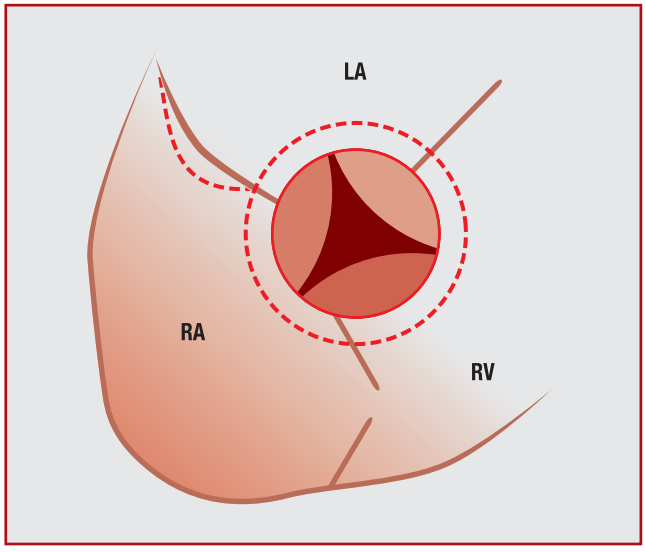

Figure 2. Schematic representation of the potential influence of aortic dilatation on the occurrence of stroke. Continuous line: a patient with normal aortic dimensions. Dotted line: a patient with an enlarged ascending aorta responsible for increased interatrial septum mobility and risk of paradoxical embolism. LA: left atrium; RA: right atrium; RV: right ventricle.

Several limitations of the present study need to be underlined. First, only patients with cryptogenic CVA and PFO were enrolled and we could not compared aortic dimensions between patients with and without PFO or with patients with CVA of known cause. However, with regard to the important prevalence of PFO in the general population, we expect that this population would be heterogeneous and that a large sample size would be necessary. Second, controls were recruited among physicians and nurses and were considered as healthy based on medical history and absence of symptoms (and normal echocardiography). No contrast study was performed and it is possible that some of them may have had PFO. However, exclusion of control subjects with PFO would have resulted in more significant differences between the groups. Third, a high proportion of ASA was observed in the present study and we cannot exclude referral bias. Fourth, we have no clear explanation for the slightly larger left ventricular diameters in PFO patients than in controls despite similar BSAs, but the difference was small. Finally, there was a significant overlap between the aortic diameter of PFO patients and healthy controls and we are certainly not implying that CVA in PFO is only related to aortic size. Furthermore, if the mean difference was approximately 3 mm, several patients had significantly enlarged aorta. Therefore, even if our sample size is limited and the study retrospective, our results should be regarded as ''proof of concept'' or as preliminary data supporting further work in this field.

Conclusion

The present study shows that aortic diameter is increased in young patients with cryptogenic CVA and PFO compared with in matched healthy subjects. Our data suggest that aortic dilatation may potentiate the risk of cerebrovascular events in patients with PFO. These preliminary results should be regarded as a proof of concept and support further research in this area.

Disclosure of interest

The authors declare that they have no conflict of interest concerning this article.

Acknowledgements

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